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Goserelin Depot in the Treatment of Premenopausal Advanced Breast Cancer

Roger W. Blamey, Walter Jonat, Manfred Kaufmann, A. Raffaele Bianco and Moise Namer

333 pre- and peri-menopausal patients with breast cancer entered a programme of open studies on the effect of goserelin. Of the 333 patients, 265 patients were entered into assessable efficacy studies. Efficacy data were analysed from 228 eligible patients receiving 3.6 mg of goserelin administered as a subcutaneous injection of a depot formulation once every 28 days. Mean serum luteinising hormone (LH) and oestradiol concentrations were suppressed by day 22 after the first injection. Subjective response occurred in 68.3% of patients assessed. Objective response (UICC criteria) occurred in 36.4% of patients and the lifetable median duration of response was 44 weeks. Responses were observed in all histological grades of tumour, and regardless of oestrogen receptor status. Treatment was well tolerated with no withdrawals due to possible adverse reactions of which hot flushes (75.9%) and loss of libido (47.4%) were commonly encountered. Goserelin provides an effective well tolerated medical alternative to ovarian ablation in the management of advanced breast cancer.
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INTRODUCTION

IT HAS long been known that certain hormones may have a profound influence on the growth of breast cancer, notably oestrogens and progestogens. In 1889 Schinzinger first suggested [1] that surgical castration could be used as a therapeutic manoeuvre in an attempt to slow the progression of advanced disease. Beatson, in 1896 reported [2] the first clinical responses to this form of treatment. Numerous reports of the results of bilateral oophorectomy in women with metastatic breast cancer have appeared in the medical literature and ovarian ablation either by oophorectomy or by irradiation of the ovaries, which was shown to be comparable, has become the established basis of hormonal manipulation in advanced pre-menopausal breast cancer. Response rates to castration have ranged from 21% to 37% [3–7].

The introduction of luteinising hormone releasing hormone (LHRH) analogues has provided an opportunity to decrease circulating oestrogen concentrations without the need for irreversible surgery.

Normally, the pituitary gland is stimulated by pulses of LHRH, producing pulsatile secretion of the gonadotrophins and maintaining cyclical gonadal activity. Chronic administration of LHRH analogues, however, causes an initial stimulation of gonadotrophin release followed by a fall in gonadotrophin secretion [8]. Treatment of pre-menopausal patients with LHRH analogues would therefore be expected to over-ride the normal pattern of LHRH release and lead to a fall in luteinising hormone (LH) and follicle stimulating hormone (FSH) concentrations and a decrease in circulating oestrogen concentrations. The potential beneficial effect of a number of these analogues in premenopausal patients with advanced breast cancer has been studied and response rates ranging from 21% to 44%, very similar to those recorded with other endocrine manipulations, have been reported [9–12].

Being polypeptides, LHRH analogues are degraded in the gastrointestinal tract if given orally and therefore parenteral administration is required. Intranasal and subcutaneous routes of administration have been used, but unless specially formulated they require administration daily (in the case of injection) or more frequently (in the case of intranasal formulations) and may therefore present compliance problems.

Goserelin (Zoladex, ICI) is a decapeptide analogue of the naturally occurring LHRH presented in a novel injectable monthly depot formulation. The formulation is already in widespread use for the treatment of prostate cancer and it has been found easy to use and acceptable to both patients and clinicians [13].

Goserelin has been investigated as a treatment for advanced breast cancer because it appeared to offer a medical alternative to ovarian ablation. This paper presents the combined results of a number of clinical trials of goserelin in advanced breast cancer in premenopausal women.

PATIENTS AND METHODS

Patients

Between 1982 and 1988 pre- and peri-menopausal patients with histologically confirmed breast cancer, considered by the treating clinician to be suitable for hormonal manipulation, were treated with goserelin in a series of clinical trials assessing efficacy and/or safety of the treatment in a number of centres throughout Europe. All patients had locally advanced (stage III) or metastatic (stage IV) disease on entry to the studies and the majority had not received previous systemic treatment either as adjuvant therapy or as initial treatment of advanced disease. Where oestrogen receptor status formed part of the inclusion criteria for the study, positive oestrogen receptor (ER) status was requested at some time in the history of the disease. However, in general most of the studies did not limit entry to only ER positive patients. All patient were pre- or peri-menopausal, (post-menopausal status was defined as having last menstruated more than 2 years prior to entry). Informed consent was obtained from all patients participating in the studies, together with local ethical committee approval at each of the centres. Patients receiving concomitant therapy known to affect levels of circulating sex hormones or assessment of response to goserelin alone were excluded, as were patients with a predicted life expectancy of less than 3 months.

Treatment

Goserelin was given as the 3.6 mg depot injected subcutaneously into the anterior abdominal wall once every 28 days by prefilled applicator. A small number of patients initially received a daily injection formulation.

Clinical trials

The 29 clinical trials were all open noncomparative studies with at least 3 months' follow-up, in which all patients were assessed regularly by clinical examination and appropriate investigations to evaluate subjective and objective response.

All the 333 patients were involved in clinical studies which were conducted and monitored in accordance with good clinical practice. The data for safety and efficacy were collected and analysed by the sponsor.

Subjective clinical response was assessed by questioning at follow-up visits about any limitations to daily activities, pain, and analgesic use that were attributable to breast cancer. Improvement in one or more of these parameters with no worsening in any was considered a subjective response.

Assessment of objective clinical response was based on the currently accepted Union Internationale Contre Cancer (UICC) criteria [14] and was graded as one of the following: complete objective regression (CR); partial objective regression (PR); no change (NC). An objective response was defined as either CR or PR.

Endocrine response was measured by determination of serum concentrations of luteinising hormone (LH) and oestradiol at follow-up visits. A serum oestradiol value of 40 pg/ml was chosen as a representative upper limit of the post-menopausal range for oestradiol in the laboratories in the study centres. The effect of treatment on menstruation was also recorded.

Any adverse events during treatment were recorded; haematology and clinical chemistry measurements were made at follow-up visits.

Statistical methods

The trials followed a standard design which facilitated pooling of the data. Pooled rates were calculated for overall subjective and objective response. In all cases the best objective response achieved during treatment was used in the analysis.

Absence of objective progression with insufficient evidence of partial objective regression was classified as "no change". "No change" was not considered to represent an objective response.

Median times to subjective and objective response, median duration of response in patients who responded and overall median time to progression (lifetable method of Kaplan and Meier [15]) were calculated.

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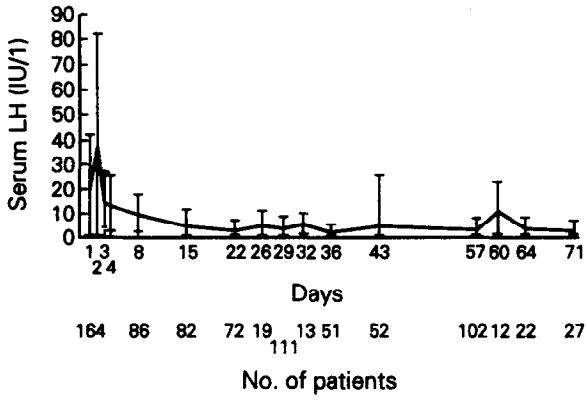

Fig. 1. Mean serum LH concentration in the first 12 weeks of therapy (with standard deviations).

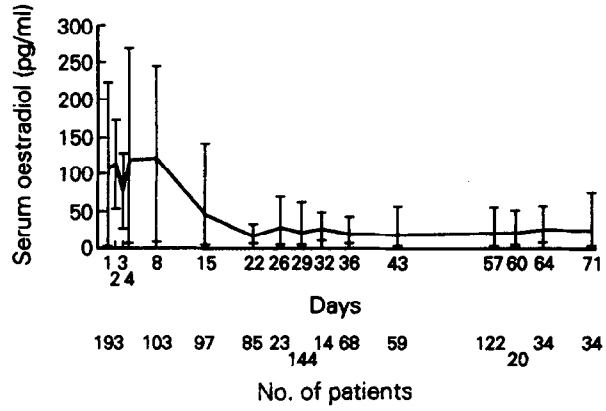

Fig. 2. Mean serum oestradiol concentration in the first 12 weeks of therapy (with standard deviations).

RESULTS

Demographic details

A total of 333 pre- and peri-menopausal patients with breast cancer were included in the 29 trials performed. Of the 333 patients, 66 were excluded from efficacy assessments because they had either received goserelin in combination with tamoxifen or had only early disease confined to the breast or did not receive the 3.6 mg depot formulation of goserelin. Thus 265 patients with advanced or recurrent breast cancer entered the studies assessing efficacy and safety. 37 of these patients were either receiving concomitant therapy that could affect response or were ineligible for other reasons (e.g. post-menopausal, no assessable disease, lost to follow-up). 228 patients were therefore assessable for efficacy.

32% (74 patients) had received previous systemic therapy for breast cancer; in the majority (60 patients) this was adjuvant cytotoxic or hormone therapy. 14 patients had received a previous systemic hormonal therapy for advanced or recurrent disease.

The mean age of the 228 patients eligible for the efficacy analysis was 41.6 years (range 24.0–55.0) and their mean weight was 65.0 kg (45.5–123.0). At the time of entry to the studies the majority (81.5%) had metastatic disease; the remaining 18.5% had advanced locoregional disease.

Safety data were collected from the total of 333 pre- and peri-menopausal patients with breast cancer, comprising 259 of the 265 entered in trials of efficacy and safety plus 74 patients entered in trials not analysed for efficacy for reasons including use of daily injection formulation of goserelin, patients with primary disease rather than advanced disease and studies involving less than 5 patients.

Endocrine response

Following an initial transient rise, the mean serum luteinising hormone (LH) was suppressed after the administration of a single 3.6 mg depot of goserelin and remained suppressed with repeated depot administration once every 28 days (Fig. 1).

Following transient rises above baseline values in individual patients during the first week, the mean serum oestradiol concentration was suppressed to a value below 40 pg/ml by day 22 after the administration of a single 3.6 mg depot of goserelin and remained suppressed with one depot given every 28 days thereafter (Fig. 2).

Menstruation

Menstruation occurred in 47% of assessed patients during the first 4 weeks of treatment but was subsequently completely suppressed in over 95% of patients.

Subjective clinical response

142 patients were symptomatic at entry to the studies. 97 (68.3%) had a subjective response to goserelin depot; the median time to subjective response was 8 weeks (range 1–52).

Objective clinical response

228 patients were eligible for assessment of objective response. 83 patients (36.4%) showed an objective clinical response (CR + PR) to goserelin depot. The median time to response among these patients was 12 weeks (range 4–49). The lifetable median duration of response was 44 weeks (range > 4–> 160) (Fig. 3).

Objective clinical responses were obtained in patients of all age groups studied, in all histological grades of tumour encountered, and regardless of the ER status of the tumour (Table 1).

Objective clinical responses were observed in patients initially presenting with advanced disease and in patients who had

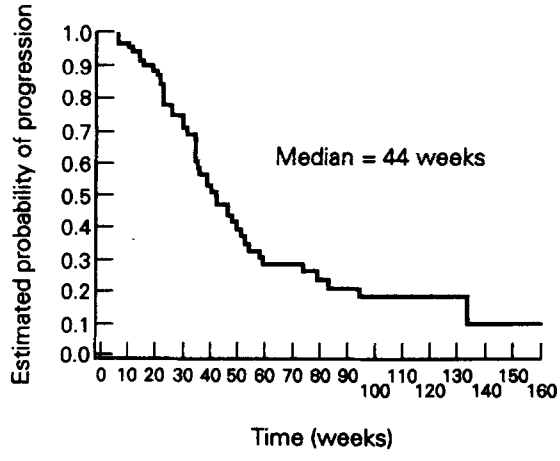

Fig. 3. Duration of response in responding patients.

Table 1. Objective clinical response rate to goserelin depot by age of patient, histological grade and ER status

Assessment	Classification		Objective response (%) (CR plus PR)
Overall	Total assessed	228	36.4
Age (years)	below 36	(37)	32.4
	36–40	(50)	38.0
	41–45	(77)	37.7
	Over 45	(64)	35.9
Tumour: degree of histological differentiation			
	High	(8)	50.0
	Medium	(85)	44.7
	Low	(69)	26.1
	Unknown	(66)	34.8
ER status			
	Positive	(102)	44.1
	Negative	(49)	30.6
	Unknown	(77)	29.9

(*n*).

developed recurrent disease following a disease-free interval (DFI) since the initial diagnosis. Responses were also observed in patients receiving previous adjuvant therapy or hormone therapy for advanced disease (Table 2).

86 patients with disease sites at entry involving major viscera such as lung and/or liver were included in the studies. Of 57 patients with disease involving lung, 16 (28%) achieved an objective response to treatment at that site, whereas 7 out of 29 patients (24%) with hepatic metastases achieved a response.

32 patients (14.0%) showed only disease progression during the studies. 163 patients (71.5%) had had progression of disease at the time of the analysis. The lifetable median time to progression was 22 weeks (range 1–> 160) in all eligible patients.

Tolerability and safety

Safety data were collected from all 333 pre- and peri-menopausal breast cancer patients included in the trials. Goserelin depot was extremely well tolerated. There were no suspected adverse reactions so severe as to require therapy to be withdrawn. The majority of the 58 possible adverse reactions reported were hot flushes and sweating (11 reports), nausea with or without vomiting (8) and dry mouth (5). In only 6 cases were the adverse events considered by the participating clinician to be severe in nature and these included one case each of headaches, hot flushes and sweating, fullness of the breasts; renal impairment and hypercalcaemia (2 cases) and a single case of oedema of the eyelids. Local bruising or intolerance to the depot injection was rare (4 cases). 7 patients experienced a worsening of signs or symptoms (predominantly pain) during the first month of therapy. In 4 cases this was associated with early progression of breast cancer. In the other 3 cases (back pain, hepatic pain and a case of hypercalcaemia with kidney dysfunction and pain) the symptoms resolved with analgesia, radiotherapy, or other specific management and treatment with goserelin was continued.

Table 2. Objective clinical response rate to goserelin depot by previous history

Factor	History		Objective response (%) (CR plus PR)
DFI (months)	0	(38)	36.8
	1–24	(108)	29.6
	25–48	(54)	48.1
	Over 48	(28)	39.3
Previous hormone therapy for advanced disease			
	No	(214)	37.4
	Yes	(14)	21.4
Previous adjuvant therapy, no previous hormone therapy for advanced disease			
	No	(154)	39.0
	Yes	(60)	33.3

(*n*).

Pharmacological effects of oestrogen suppression were commonly encountered, such as hot flushes (75.9%) and loss of libido (47.4%). Others such as vaginal dryness and mood disturbance were less commonly encountered (< 2%).

Of the 13 deaths reported during the study, only 3 were attributed to causes other than breast cancer alone. These were: (i) pulmonary embolism after surgical decompression of spinal metastases, (ii) pneumonia in the presence of disseminated disease, (iii) acute pulmonary oedema in a patient with a history of heart disease requiring digoxin and frusemide.

DISCUSSION

The data described here, which extend previous reports [16, 17] represent one of the largest coordinated programmes of studies of the treatment of advanced breast cancer in pre- and peri-menopausal women. The clinical response rate in pre- and peri-menopausal women with advanced breast cancer following surgical ablation of the ovaries is in the range 21–37% [3–7]. The objective response rate (CR plus PR) of 36.4% achieved with goserelin depot as an initial treatment for advanced breast cancer in pre- and peri-menopausal women compares very favourably with this range, and with the response rates achieved in similar patient groups with the anti-oestrogen tamoxifen (around 30%) with the same duration of response of around 12 months.

Higher response rates were observed in the subgroups of patients with tumours that were ER positive and those that were well differentiated histologically, but responses were also achieved in ER negative and poorly differentiated tumours.

It is noteworthy that even among the small number of patients (14) who had previously received hormonal therapy for advanced disease, an overall objective response rate of 21.4% was achieved.

Oophorectomy is an irreversible procedure. The pharmacological effects of surgical castration are as likely to affect those patients who do not receive any clinical benefit from the operation as those who do respond. Bearing in mind the response rate of 21–37%, a significant proportion of patients are also exposed to the risk of peri- and post-operative morbidity and mortality without the benefit of clinical response.

Ovarian ablation by irradiation produces similar pharmacological effects, as well as the generalised effects of radiation. Furthermore, irradiation may take 6 weeks or more to suppress ovarian oestrogen production [18].

Anti-oestrogen therapy provides an alternative means of treating patients with oestrogen-dependent breast cancer [3, 4]. In a proportion of patients, however, it does not induce amenorrhoea, and elevation of circulating oestrogen concentrations has been reported [19, 20] with a possibility that this may limit those responses observed.

The results observed in this group of pre- and peri-menopausal patients with advanced or recurrent breast cancer treated with goserelin support the preliminary findings reported with other LHRH analogues [9–12]. LHRH analogues do appear to provide an effective, well tolerated alternative to ovarian ablation in the palliative treatment of these patients, avoiding the need for surgical intervention. Studies are currently underway to investigate whether the combination of goserelin and tamoxifen (i.e. total oestrogen blockade) has any additional benefit when compared with goserelin alone.

The depot formulation of goserelin given once every 28 days provides a convenient and reliable means of administering such therapy to those patients in whom hormone manipulation is indicated.

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